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Original Article

Correlation of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$ T-Cells Percentage and Serum MMP-9 Level with Cognitive Dysfunction among Systemic Lupus Erythematosus Patients

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ABSTRACT

Background: *'Lupus brain fog'* is a phenomenon of cognitive function decline in SLE patients. Premature immunosenescence in SLE was presumed to play a significant role in the mechanism of cognitive dysfunction.

Aim: To prove the correlation between the terminally-differentiated $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, and $CD8^+KLRG1^+$ T-Cells & serum MMP-9 levels with cognitive dysfunction in SLE patients.

Methods: There were53 women SLE were conducted to perform MMSE and MoCA-Ina tests to evaluate cognitive function. Immunosenescence was observed by measuring the terminally-differentiated $CD4^+CD57^+$, CD8+CD57+, $CD4^+KLRG1^+$, and $CD8^+KLRG1^+$ T-Cells, which were measured by flowcytometry. In addition, MMP-9, an enzyme produced by terminally-differentiated T-Cells, was measured using ELISA.

Results: SLE patients with cognitive dysfunction based on MMSE and MoCA-Ina test had higher percentage of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$ T-Cells and serum MMP-9 level compared to patients with normal cognitive function. $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$ T-Cells percentage and serum MMP-9 level showed negative correlation with both MMSE scores (r = -0.286; r = -0.447; r = -0.279; r = -0.537; r = -0,411) and MoCA-Ina scores (r = -0.454; r = -0.539; r = -0.435; r = -0.535; r = -0.648). Meanwhile, percentage of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$ and $CD8^+KLRG1^+$ T-Cells showed positive correlation with serum MMP-9 level (r = 0.292; r = 0.414; r = 0.449; r = 0.374).

Conclusion: Expansion of $CD4^+CD57^+$, $CD8^+C57^+$,$CD4^+KLRG1^+$, $CD8^+KLRG1^+$ terminally differentiated T-Cells& increase of serum MMP-9 level are correlated with cognitive dysfunction in SLE patients.

Keywords: Systemic Lupus Erythematosus, Immunosenescence, Cognitive Dysfunction

INTRODUCTION

The clinical manifestation of degeneration in Systemic Lupus Erythematosus (SLE) showed a similar profile as in the elderly population, including a cognitive function decline.[1–3] The cognitive dysfunction in SLE, *'lupus brain fog',* is reported in 20-80% of SLE patients. Cognitive dysfunction is correlated

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with decreased quality of life, social participation, and increased stress, anxiety, and depression. This condition can reduce patient compliance in carrying out treatment programs, thus worsening the prognosis of SLE disease. In addition, cognitive dysfunction in SLE will lead to higher medical costs. Therefore, early detection and appropriate treatment of cognitive dysfunction are challenges in holistic SLE management.[4,6–8] Although the case rate is high, the specific management of cognitive dysfunction in SLE is still minimal due to limited studies that can clearly explain the causes and underlying pathophysiological mechanisms.[3–5]

Immunosenescence is a phenomenon of the aging process that occurs in the immune system. Immunosenescence in adaptive immunity affects T lymphocytes both CD4+ and CD8+. Under these conditions, cells did not express costimulatory molecules such as CD27 and CD28, and expressed markers such as killer cell lectin-like receptor sub family G (KLRG1) and CD57. Therefore, KLRG1 and CD57 are considered markers of terminal differentiation or cellular senescence. These terminally differentiated cells have an inflammatory phenotype that causes an increase in the formation of cytokines and pro-inflammatory enzymes such as IL-6, TNFα, PGE2, and MMP-9. This inflammatory state is called *inflammaging*, which is a characteristic feature of immunosenescence.[9] Several studies have demonstrated a neuro-immunological relationship and the role of immunosenescence in inducing accelerated brain aging, memory loss, and other neuro-degenerative manifestations.[10] In SLE patients, early immunosenescence is a key mechanism in the neuropath logical processes underlying cognitive dysfunction. Several studies have shown an inverse correlation between increased pro-inflammatory cytokines in the peripheral circulation and memory performance in SLE patients.[4,11,12] Similarly, MMP-9 is well known to cause damage to the blood-brain barrier and mediate cognitive dysfunction.[4]

This study determines the relationship among the expansion of CD4+CD57+, CD8+C57+, CD4+KLRG1+, CD8+KLRG1+ terminally differentiated T-Cells and MMP-9with cognitive dysfunction in SLE patients.

METHODS

Design and Subjects of Study

The subjects of this study were 53 female patients aged 16-45 years who met the SLE classification criteria based on the 2012 Systemic Lupus International Collaborating Clinics (SLIML) and an active SLEDAI score >3. Severe infection, pregnancy or lactation, impaired consciousness, or a history of cognitive dysfunction before SLE diagnosis were exclusion criteria for study subjects. All subjects were active SLE patients at the Rheumatology polyclinic, Department of Internal Medicine, RSUD Dr. Saiful Anwar Malang. All subjects in this study had signed an informed consent form, and all of the study protocols were approved by the Ethics Commission of RSUD Dr. Saiful Anwar Malang No. 400/120/K.3/302/2017.

Basic Data Collection and Blood Collection

Data were obtained from interviews and direct examination of patients, including demographic data, clinical data (onset of disease, history of clinical manifestations since first diagnosed, current complaints, and medical history). In addition, a total of 10 ml of venous blood was taken in a tube with heparin

for PBMC isolation, a plain tube for blood serum chemistry (C-reactive protein (CRP), antibody anti-dsDNA, levels of complement C3 and C4), and an EDTA tube for a complete blood count.

Examination of Cognitive Function

Cognitive function was assessed with the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment Indonesian version (MoCA-Ina) that previous studies have validated. The work of the two tests was carried out independently by the study subjects with direct direction and supervision from the study team. It was declared cognitive dysfunction if the MMSE score <24 or MoCA-Ina score <26 or both.[13,14]

Isolation of Peripheral Blood Mononuclear Cells (PBMC)

PBMCs were separated from whole blood by centrifugation of 1600 g and using Ficoll gradient Lymphoprep (Stemcell Technology Catalog no.07801). Then, the PBMCs were washed and divided into aliquots for immunopheno typing assays.

Measurement of the percentage of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, and $CD8^+KLRG1^+$ T-Cells

PBMCs for phenotyping were blocked by 2% mouse serum before being labeled with three panels of the fluorochrome-conjugated (FITC) monoclonal antibodies to the surface markers studied, namely CD3, CD4 or CD8, and CD57 or KLRG1: anti-human CD3 antibody (Biolegend; cat number 300405), PerCP anti-human CD4 antibody (Biolegend; cat number 300527), PerCP anti-human CD8 antibody (Biolegend; cat number 344707), PE anti-human CD57 antibody (Biolegend; cat number 830795) and PE anti-human KLRG1 (Biolegend; cat number 367704). Cells were fixed with paraformaldehyde. Flowcytometry was performed using BD Cell Quest (BD FACS Calibur) software. Measurements based on 10,000 cells, and the results were obtained as a percentage (%).

Measurement of Serum MMP-9 Enzyme Levels

MMP-9 enzyme levels were measured from serum, using the ELISA method by Biolegend kit (cat number 444907). ELISA measurements were performed according to the manufacturer's protocol.

Statistical Analysis

Overall statistical tests & table generation were performed using IBM SPSS for Windows version 23.0. Comparisons among groups were analyzed using an independent (unpaired) parametric T-test, while non-parametric data were analyzed using the Mann-Whitney test. Comparison between categorical variables were using chi-square test. The correlation between T-Cells and serum MMP-9 levels with cognitive dysfunction based on MMSE and MoCA-Ina scores in SLE patients was assessed by Pearson's test for parametric data and Spearman's test for non-parametric data. The statistical test is significant if the p-value <0.05. In addition, parametric data is presented in the form of mean ± SD, while non-parametric data is presented in the median (25-75th percentile).

RESULTS

Characteristics of Study Subjects

A total of 53 subjects with SLE patients aged 28.3 ± 6.5 years old, with the onset of clinical symptoms related to SLE were 24 ± 5.8 years. Neuropsychiatric manifestations of SLE were found in 6 (11.3%) study subjects.

Cognitive function examinations were performed using different instruments, namely MMSE and MoCA-Ina, which showed median values of 24 (20-26) and 26 (24-28), respectively. The primary characteristics of the study subjects are presented in **Table 1.**

From 53 study subjects, 24 patients (45.3%) LES with cognitive dysfunction were found based on the results of the MMSE test, and 23 patients (43.4%) based on the results of the MoCA-Ina test. The number of patients with a history of neuropsychiatric SLE events was significantly higher in the subjects of SLE patients with cognitive dysfunction based on the results of the MMSE test compared to the group without cognitive dysfunction (20.8% vs. 3.4%, p = 0.047). However, duration, medication history, educational history, socioeconomic background, CRP levels, increased anti-dsDNA and decreased complement did not provide significant differences between the two groups, based on the results of the MMSE and MoCA-Ina (**Table 2** and **3**).

Table 1. Baseline Characteristics of Study Subjects

Variable	Mean/Median/ n (%)
Age (year)	28.3 ± 6.5
Onset (year)	24.0 ± 5.8
Duration (month)	24 (24-78)
ClinicalManifestation	
• Neuropsychiatry SLE	6 (11.3)
• Arthritics	14 (26.4)
• Myositis	1 (1.9)
• Mucocutaneous manifestation	23 (43.4)
• Vasculitis	13 (24.5)
• Nephritis	25 (47.2)
• Serositis	10 (18.9)
• Thrombocytopenia	4 (7.5)
• Leukopenia	15 (28.3)
Cognitive Test	
• MMSE Score	24 (20-26)
• MoCA-Ina Score	26 (24-28)
Education Background	
• ≤ Upper secondary education	35 (66.0)
• ≥ Undergraduate	18 (34)
Socioeconomics	
• Working	14 (26.4)
• Paid <1.500.000/month (IDR)	47 (88.7)
• Paid ≥1.500.000/month (IDR)	6 (11.3)
Therapy	
• steroid	48 (90.5)
• Chloroquine	13 (81.1)
• Cyclophosphamide	3 (5.6)
• Azathioprine	21 (39.6)
• Mycophenolate mofetil	9 (16.9)
CRP (mg/dL)	0.19 (0.09-0.80)
Anti-dsDNA (IU/mL)	85.10 (38.60–198.40)
CD4/CD8 Ratio	0.8 (0.6-1.2)
IRP positive	33 (62.2)
SLEDAI Score	6 (4-13)

MMSE: Mini Mental State Evaluation; CRP: C Reactive Protein; SLE: Systemic Lupus Erythematosus; IDR: Indonesian Rupiah; IRP: Immune Risk Profile

Table 2. Differences in Characteristics of Study Subjects based on MMSE Test Results

Variable	SLE Patients with Cognitive Dysfunction (n=24)	SLE Patients without Cognitive Dysfunction (n=29)	p
Duration (month)	33 (21.7-84)	24 (24-66)	0.971
NP SLE history, n (%)	5 (20.8)	1 (3.4)	0.047**
Treatment, n (%)			
• Steroid	21 (87.5)	27 (93.1)	0.487
• Chloroquine	20 (83.3)	23 (79.3)	0.709
• Cyclophosphamide	1 (4.2)	2 (6.89)	0.669
• Azathioprine	8 (33.3)	13 (44.8)	0.394
• Mycophenolate mofetil	5 (20.8)	4 (13.7)	0.497
Education Background, n (%)			
• ≤ Upper secondary education	17 (70.8)	18 (62.1)	0.502
• ≥ Undergraduate	7 (29.2)	11 (37.9)	
Socioeconomics, n (%)			
• Paid < 1.500.000/month (IDR)	22 (91.7)	25 (86.3)	0.532
• Paid ≥ 1.500.000/month (IDR)	2 (8.3)	4 (13.7)	
CRP (mg/L)	0.25 (0.11-1.35)	0.12 (0.08–0.7)	0.122
Increasing anti-dsDNA, n (%)	16 (66.7)	22 (75.9)	0.459
Decreasing complement, n (%)	0 (0.0)	0(0.0)	n/a

**) Cognitive dysfunction was based on MMSE scores < 24; **) The differences between the two groups were statistically significant (p < 0.05); MMSE: Mini Mental State Evaluation; CRP: C Reactive Protein; SLE: Systemic Lupus Erythematosus; IDR: Indonesian Rupiah*

Table 3. Differences in Characteristics of Study Subjects based on MoCA-Ina Test Results

Variable	SLE Patients with Cognitive Dysfunction (n=24)	SLE Patients without Cognitive Dysfunction (n=29)	p
Duration (month)	30 (24-84)	24 (22-5.60)	0.676
NP SLE history, n (%)	4 (17.3)	2 (6.7)	0.222
Treatment, n (%)			
• Steroid	20 (87.0)	28 (93.3)	0.431
• Chloroquine	18 (78.3)	25 (83.3)	0.640
• Cyclophosphamide	0 (0.0)	3 (10.0)	0.118
• Aazathioprine	6 (26.1)	15 (50.0)	0.078
• Mycophenolate mofetil	6 (26.1)	3 (10.0)	0.122
Education Background, n (%)			
• ≤ Upper secondary education	17 (73.9)	18 (60.0)	0.289
• ≥ Undergraduate	6 (26.1)	12 (40.0)	
Socioeconomics, n (%)			
• Paid < 1.500.000/ month (IDR)	21 (91.3)	26 (86.7)	0.597
• Paid ≥ 1.500.000/ month (IDR)	2 (8.7)	4 (13.3)	
CRP (mg/L)	0.20 (0.09-0.80)	0.16 (0.09-0.82)	0.706
Increasing anti-dsDNA, n (%)	18 (78.3)	20 (66.7)	0.353
Decreasing complement, n (%)	0 (0.0)	0 (0.0)	n/a

**) Cognitive dysfunction was based on MMSE scores < 24; *) Cognitive dysfunction based on MoCA-Ina scores < 2; IDR: Indonesian Rupiah*

Comparison of Percentage of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$ T-Cells, and Serum MMP-9 Levels by Functional Cognitive Status of SLE Patients

Terminally-differentiated T-Cells were represented with CD4, CD8 T-Cells expressing CD57, and CD4 T-Cells expressing KLRG1. The percentage of $CD4^+CD57^+$ T-Cells was found to be significantly higher in the SLE patient group with cognitive dysfunction when compared to the group without cognitive dysfunction, as assessed by the MMSE test [1.99% (0.73-3.25) vs. 0.86% (0.75-1.411); p = 0.006] and MoCA-Ina [2% (0.78-3.32) vs. 0.8% (0.48-1.33); p = 0.005]. Similar results were also obtained for the percentage of $CD8^+CD57^+$ T-Cells, which were significantly higher in the SLE patient group with cognitive dysfunction based on the results of the MMSE test (13.44 ± 6.12% vs. 8.12 ± 6.26%; p = 0.000) and MoCA-Ina (14.41 ± 6.41% vs. 7.55 ± 5.29%; p = 0.000) when compared with the group without cognitive dysfunction.

The percentage of $CD4^+KLRG1^+$ T-Cells was also found to be significantly higher in the SLE patient group with cognitive dysfunction compared to the group without cognitive dysfunction, as assessed by the MMSE test [4.38% (2.28-5.65) vs. 1.67% (1-3.24); p = 0.003] and MoCA-Ina [4.77% (2.68-5.68) vs. 1.57% (1.07-3.15); p = 0.004]. Similar results were also obtained for the percentage of $CD8^+KLRG1^+$ T-Cells, which were significantly higher in the SLE patient group with cognitive dysfunction based on the results of the MMSE test (15.82 ± 6.93% vs. 9.37 ± 5.71%; p = 0.000) and MoCA-Ina (16.58 ± 6.61% vs. 9.37 ± 5.71%; p = 0.000) and MoCA-Ina (16.58 ± 6.61% vs. 9.01 ± 5.42%; p = 0.000) compared with the group without cognitive dysfunction.

The MMP-9 enzyme was another variable observed in this study. MMP-9 is a terminally-differentiated T-Cells product and is expected to mediate cognitive dysfunction in SLE patients. Serum MMP-9 enzyme levels in SLE patients with cognitive dysfunction were found to be significantly higher than in SLE patients without cognitive dysfunction, based on the results of the MMSE test [2669.75 ± 953.46 ng/ml vs. 1861.58 ± 628.73 ng/ml, p=0.000] and MoCA-Ina [2888.78 ± 769.33 ng/ml vs. 1720.59 ± 580.34 ng/ml, p=0.000]. The percentage comparison of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$ T-Cells, and serum levels of MMP-9among groups of study subjects are presented in **Figure 1**.

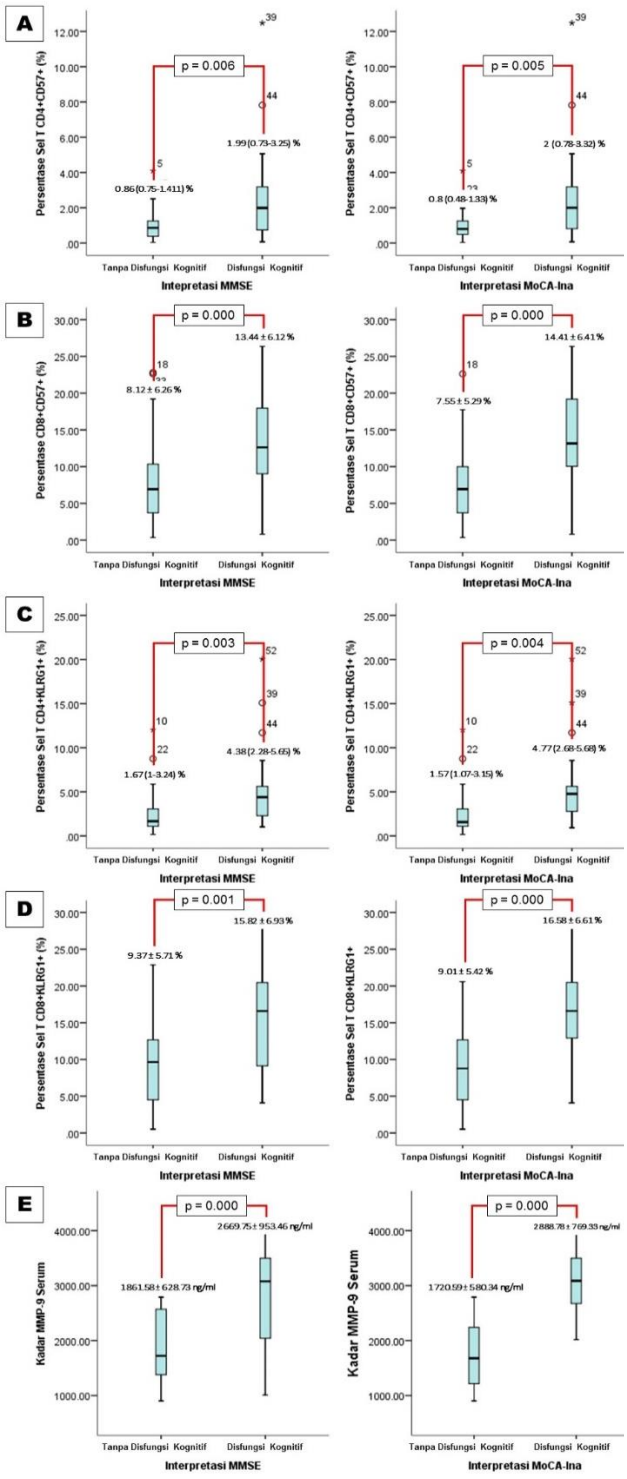

Figure 1. The percentage comparison of $CD4^+CD57^+$T-Cells(A) $CD8^+CD57^+$T-Cells,(B) $CD4^+KLRG1^+$T-Cells, (C) $CD8^+KLRG1^+$T-Cells (D) Serum levels of MMP-9 (E) in SLE patients with and without Cognitive Dysfunction *(data presented in the median form in Figures 2.A and 2 .C and in the form of the mean in Figures 2.B,2.D and 2.E)*

Correlation among the percentage of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$, and serum levels of MMP-9with Cognitive Function in SLE Patients

The relationship between immunosenescence in SLE patients and the occurrence of cognitive decline was assessed by correlation test between the percentage of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$ and $CD8^+KLRG1^+$ T-Cells with MMSE and MoCA-Ina scores **(Figures 2A, 2B, 2C & 2D)**. The results of the Spearman test showed that the percentage of $CD4^+CD57^+$ T-Cells had a weak negative correlation with the MMSE score (r = -0.286; p = 0.038) and a moderate negative correlation with the MoCA-Ina score (r = -0.454; p = 0.001). A moderate negative correlation was also found between the percentage of $CD8^+CD57^+$ T-Cells and the MMSE score (r = -0.447; p = 0.001), while for the MoCA-Ina score, this variable showed a strong negative correlation (r = -0.539; p = 0.000) From the test, it was also found that the percentage of $CD4^+KLRG1^+$ T-Cells had a weak negative correlation with the MMSE score (r= -0.279; p=0.043) and a moderate negative correlation with the MoCA-Ina score (r= -0.435; p=0.001). A strong negative correlation was found among the percentage of $CD8^+KLRG1^+$ T-Cells with the MMSE score (r= -0.537; p=0.000), and with the MoCA-Ina score (r= -0.535; p=0.000).

The relationship between serum levels of MMP-9, a product produced by terminally-differentiated T-Cells, and cognitive function also showed a significant negative correlation **(Figure 2E).** The results of statistical analysis showed a moderate negative correlation between serum levels MMP-9 and the MMSE score (r = -0.411; p = 0.002) and a strong

negative correlation with the MoCA-Ina score (r = -0.648; p = 0.000).

Correlation among Percentage of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$T-Cells, and Serum MMP-9 Levels

MMP-9 is a terminally-differentiated T-Cells product and is suspected of mediating cognitive dysfunction in SLE patients through the immunosenescence pathway. The correlation test among the percentage of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$ T-Cells, and serum MMP-9 levels was carried out to assess the correlation and clarify the position of each of these variables in Pathophysiological pathway mechanisms of cognitive dysfunction in SLE patients. Statistical analysis results showed that the percentage of $CD4^+CD57^+$T-Cells had a weak positive correlation of MMP-9 serum (r = 0.292; p = 0.034) and that $CD8^+CD57^+$ T-Cells had a moderately positive correlation of serum MMP-9 (r = 0.414; p = 0.002) as shown in **Figure 2F**. Whereas statistical analysis results showed that the percentage of $CD4^+KLRG1^+$ and $CD8^+KLRG1^-$ T-Cells had a moderately positive correlation with serum MMP-9 levels (r = 0.449; p = 0.001 & r = 0.374; p = 0.006) as shown in **Figure 2G**.

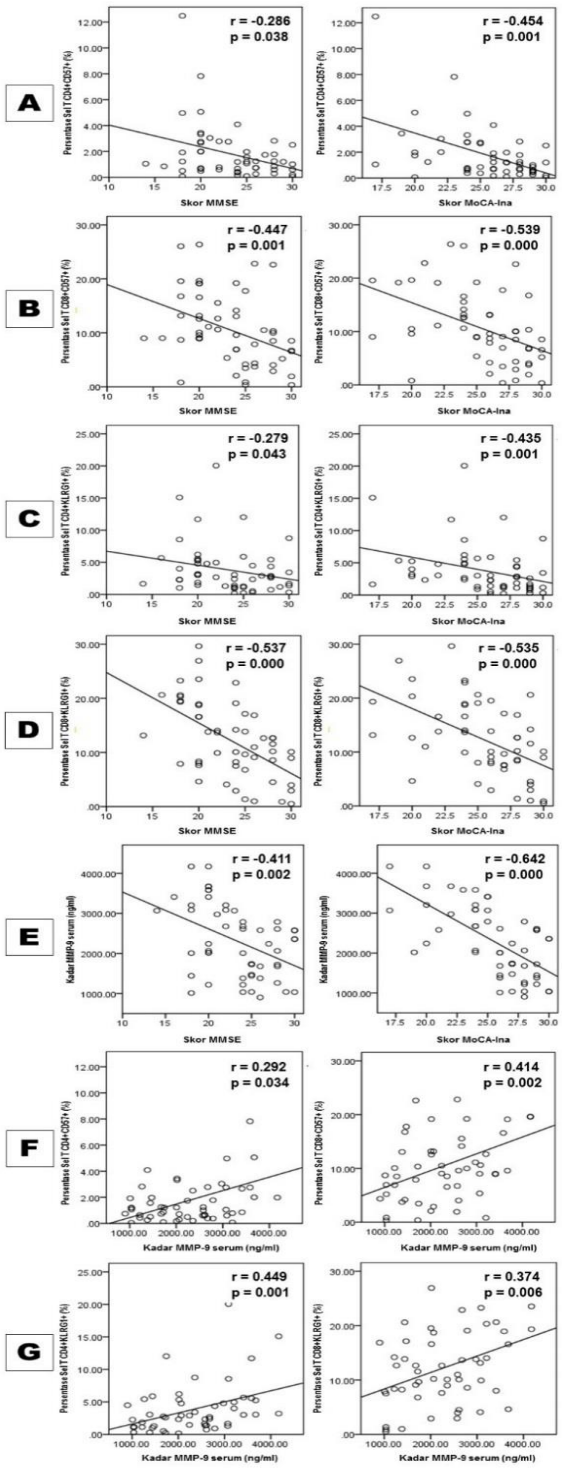

Figure 2. Correlation between MMSE and MoCA-Ina scores with The Percentage of CD4 $^+CD57^+$ T-Cells (A), $CD8^+CD57^+$ T Cell (B), $CD4^+KLRG1^+$ T Cell (C), $CD8^+KLRG1^+$ T-Cells (D) Serum MMP-9 Levels (E) in SLE Patients; and the correlation among serum MMP-9 levels with the percentage of $CD4^+CD57^+$, $CD8^+CD57^+$ T-Cells (F) and the percentage of $CD4^+KLRG1^+$, $CD8^+KLRG1^+$ T-Cells(G)

DISCUSSION

Our study shows that SLE patients with Cognitive dysfunction show a different manifestation of peripheral immunity from normal cognitive SLE patients. Patients with cognitive dysfunction showed a significantly higher percentage of $CD4^+CD57^+$T-Cells and a negative correlation between the percentage of $CD4^+CD57^+$T-Cells and cognitive function. Expression of CD57 on CD4 T-Cells causes characteristic changes that make these cells classified as cytotoxic 1 helper T-Cells. These cells showed the ability of cytolytic cells and correlated with the expression of cytolytic granules, granzyme B, and perforin, which are cytotoxic molecules and induce tissue damage, both of which are physiologically only possessed by NK cells and cytotoxic CD8+ cells.[15] These cells are the predominant component involved in neurodegenerative and neuro-inflammatory diseases through pro-inflammatory cytokine pathways and direct effects of cytotoxicity on neuronal cells.[10]

Another study by Magistrelli *et al*. revealed that the number of CD4 T-Cells present in peripheral blood circulation had an inverse relationship with cognitive function in patients with Parkinson's disease, assessed using the Adden brooke Cognitive Examination (ACE-R).[16] SLE is a chronic inflammatory disease in which the peripheral immune profile also shows pro-inflammatory properties, thus giving a similar manifestation to Parkinson's disease.

In this study, $CD8T^+CD57^+$T-Cells were also significantly higher in SLE patients with cognitive dysfunction than the normal cognitive group. Recent studies have shown that the expansion of $CD8^+CD57^+$T-Cells is associated with the phenomenon of immunosenescence, and the presence of these cells is associated with inflammatory activity due to the ability to secrete pro-inflammatory cytokines, cytotoxic molecules such as granzyme and perforin, proliferate and persist for a longer period due to resistance to apoptosis, in which also known as NK-like $CD8^+$ Effector Memory T Cell.[17,18]

This study also showed that the percentage of $CD4^+KLRG1^+$T-Cells was significantly higher in SLE patients with cognitive dysfunction and that there was a negative correlation between the percentage of $CD4^+KLRG1^+$T-Cells and cognitive function. This is consistent with the results of a study by Pellicano *et al*, where KLRG1 on CD4 T-Cells were also higher in patients with Alzheimer's disease, where this disease is characterized by decreased cognitive function.[19]

Several studies found that KLRG1 expression on CD4 T-Cells correlated with an increase in interferon-gamma and cytotoxic responses.[20–22] KLRG1 also induces phosphorylation of N-cadherin in which affecting down regulation of the N-cadherin. N (neuronal)-cadherin found in brain tissue functions to maintain tissue integrity by being a liaison between cells. Therefore, if there is a down regulation due to KLRG1, it will cause the relationship between these cells to be disrupted and not optimally carry out their functions.[23,24]

Whereas, KLRG1 expression on CD8 T-Cells, a study conducted by Novelli found that KLRG1 expression increased with age, with more than 90% of its expression on CD8 T-Cells in individuals over 65 years of age.[25] From a study conducted by Wheeler, it was found that CD8+KLRG1 T-Cells were increased in patients with age-related cognitive dysfunction.[26]

The decline in cognitive function is

associated with the expansion of $CD4^+CD57^+/KLRG1^+$ T-Cells and $CD8^+CD57^+/KLRG1^+$ T-Cells related to the migration of these cells into brain tissue. It is thought that in inflammatory conditions such as aging or autoimmune disease, peripheral T-Cells can cross the brain barrier and induce neuronal damage. This allegation is supported by Gamechu and Bentivoglio study that found that the T-Cells in peripheral circulation can pass through the blood-brain barrier in patients with normal aging. Thus, the blood-brain barrier's structural and functional disruption may occur in normal aging associated with a pro-inflammatory phenotype in old age. Leukocyte transmigration, which involves many steps, occurs primarily in postcapillary venules and appears to involve paracellular routes and transcellular diapedesis. This cell migration is primarily controlled by the expression of adhesion molecules, chemokines, and their receptors. T-Cells that have crossed the barrier will then activate endothelial cells by releasing cytokines, which then induce or increase the expression of cell adhesion molecules.[27] This mechanism accelerates the inflammatory cascade many-fold. The migration of T-Cells into the brain is also facilitated by chemokines secreted by reactive astrocytes, including monocyte chemotactic protein (MCP)-1 and macrophage inflammatory protein-1 (MIP)-1α. On the other hand, the matrix metalloproteinase (MMP), secreted by activated T-Cells and macrophages, can destroy the extracellular matrix components as an effector inflammatory response after the migration of T-Cells.[28] The changing phenotype of senescent T-Cells, cytotoxic and pro-inflammatory, allegedly underlie neuro inflammation and induces neuronal damage through a mechanism commonly referred to as *inflammaging.*[1,10,29] Moreover, the study by Kadowaki *et al*. found that when KLRG1 binds to its ligand, N-cadherin on neurons, it causes down regulation of the N-cadherin.[30]

MMP is a molecule that mediates the migration of peripheral T-Cells to the brain parenchyma, with its role in disrupting tight junctions' blood-brain barrier. Our study also found that serum MMP-9 levels were significantly higher in SLE patients with cognitive dysfunction, compared to the normal cognitive group. The study conducted by Ianetta *et al*. explained that MMP-9 levels were correlated with lesions on MRI and multiple sclerosis disease activity. The same study also showed an increase in serum MMP-9 levels that correlated with the expansion of senescent CD4 and CD8 T-Cells. MMP-9 also plays a role in neuronal damage by demyelinating neuronal axons and causing cell death by excitotoxic mechanisms.[31–33]

CONCLUSION

Based on the results of this study coupled with data from previous studies, it can be concluded that immunosenescence has an important role in the pathogenesis of cognitive dysfunction in SLE patients. The expansion of terminally differentiated effect $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, and $CD8^+KLRG1^+$ T-Cells correlates with cognitive dysfunction in SLE patients, both through their direct cytotoxicity potential and through their intermediary increased production of the enzymeMMP-9. Further studies also need to be conducted to assess the presence and correlation of $CD4^+CD57^+$, $CD8^+CD57^+$, $CD4^+KLRG1^+$, $CD8^+KLRG1^+$, and MMP-9 in cerebrospinal fluid with cognitive function in

order to clearly describe the involvement in causing cognitive dysfunction in SLE patients.

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